Message

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Sent: 12/11/2012 3:29:15 PM
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Subject: NEWS UPDATES: Industry Queries NTP Science Review Plan EPA May Use For IRIS Program (Inside EPA)

Industry Queries NTP Science Review Plan EPA May Use For IRIS Program

Posted: December 10, 2012

Chemical industry and small business advocates are criticizing a lack of transparency in the National Toxicology Program's (NTP) new systematic-review approach for improving risk and environmental health analyses -- a method EPA officials are weighing as a model to improve the agency's Integrated Risk Information System (IRIS) program.

The NTP method would establish a seven-step process for bolstering literature searches and enhancing reviews of risk and environmental health data in order to boost the validity of conclusions on key scientific data.

Ahead of a Dec. 11 meeting where NTP will present the approach to its Board of Scientific Counselors (BSC), the American Chemistry

Council (ACC) says it supports the development of a "systematic" process for reviewing risk literature and other data and a weight-of-evidence system for evaluating scientific studies for NTP and IRIS. However, a spokesman for the group says, "Our concern lies with having sufficient time to provide input" on the approach. In a recent letter to NTP, the group says the existing method could lead NTP to rely on poor quality data.

Similarly, the Small Business Administration's (SBA) Office of Advocacy in a Dec. 6 letter to NTP urges it to delay making a decision on the new approach in order to allow more time for the public to weigh in. SBA "respectfully requests that the BSC extend time for consideration of the Systematic Approach in order to allow for a more robust public comment process," says the letter from Winslow Sargeant, chief counsel for SBA advocacy.*Relevant documents are available on InsideEPA.com. (Doc ID: 2418574)*

In response to the concerns, Andrew Rooney, deputy director of NTP's Office of Health Translation and Assessment, said through a spokeswoman that NTP "welcomes all public comments. Each public comment is placed on the NTP web site, shared with our Board of Scientific Counselors and taken into consideration by NTP."

During an earlier Nov. 27 interview with *Inside EPA*, Rooney said that scientists at NTP -- a program within the National Institute of Environmental Health Sciences (NIEHS) -- have been developing what they call "systematic review" over the past year. The multi-step approach incorporates literature search, consideration of quality of information and data extraction techniques to glean a scientific basis for answering a particular question, he said.

Ken Olden, the new director of EPA's National Center for Environmental Assessment, has said systematic review could be helpful in improving the agency's influential, but often criticized, IRIS program.

During a Dec. 6 interview, Olden said that he has asked a deputy to begin putting together a workshop on systematic review to inform EPA on how the approach works, and how it could potentially improve IRIS chemical assessments. Olden said he want to hear from a diverse group of experts on systematic-review topics.

But Olden also stressed the need for outside groups to comment on it, saying the approach "needs public vetting [before EPA adopts it]. I'd like to set up a full day where we talk about the pros and cons of different approaches," he said in the interview. "Then after that, we would decide which is the way for us to go."

He added, "If I was developing it, and we are leaning heavily on what others have done, at some point we have to get the stakeholders' input. . . . The question is when [to seek that input]."

Olden suggested that such discussions are more substantive when the public has a draft document to respond to, and expressed confidence that NTP would include public comment before finalizing its approach.

Linda Birnbaum, the director of NTP and NIEHS, has suggested that systematic review could help IRIS staff respond to a number of criticisms lobbied at the program, according to her remarks at a Nov. 13 public meeting seeking suggestions on how to improve IRIS. For example, IRIS critics have long claimed that agency staff cherry-pick the studies used to calculate quantitative risk estimates to make chemicals' risks appear more dire.

NIEHS' Office of Health Assessment and Translation over the past two years "has spent considerable effort in examining various existing systematic-review models as currently carried out by Agency for Healthcare Research and Quality and a collaboration called GRADE, among others," Birnbaum said.

"The focus of this is really, or has been based upon, evidence-based medicine," Birnbaum said at the meeting. "It is important to implement elements of systematic review into the literature-gathering and quality-evaluation steps. This not only provides documentation that the appropriate literature has been searched and collected; two, that information was appropriately extracted from the literature; and three, also provides a record that allows one to better understand how information has been integrated in the process of reaching conclusions."

Rooney in the interview said a literature search "enhances the transparency of a literature-based evaluation. . . . A transparent structure for the literature search, determining relevance, extracting data and determining its quality." While it "provides a transparent structure, it doesn't eliminate the need for expert judgment."

NTP released a draft of its systematic-review approach in August, seeking comments from a work group of BSC members and others with expertise in systematic review. Ahead of the Dec. 11 meeting, NTP released the work group's report of recommendations, as well as a revised version of its draft systematic-review approach.

The latest draft explains the seven-step approach NTP has developed, beginning with "scop[ing] and focus[ing] the topic," leading to the creation of "a draft protocol [that] is developed that outlines the proposed approach to answer the specific question or questions to be addressed in the evaluation."

The next step in the approach is the literature search. NTP has included a number of details that appear to address common industry concerns that it is unclear how NTP and IRIS select studies for inclusion in their assessments. NTP's latest draft says, "A comprehensive search of the primary scientific literature is performed . . . with sufficient details of the search strategy documented in the protocol such that it could be reproduced."

The third step entails data extraction from the studies selected through the literature search. The latest draft of NTP's approach

explains, "Relevant data are extracted from individual studies selected for inclusion using separate template forms for human, animal, and *in vitro* studies that are customized as needed for specific evaluations."

Next, the approach reviews the quality of each study's design through a pre-defined process. The draft says, "The risk of bias tool . . . uses specific questions under five domains (selection, performance, attrition, detection, and reporting bias). . . . For each study outcome, all of the applicable questions are answered with one of four options (definitely low, probably low, probably high, or definitely high risk of bias) . . . following pre-specified criteria detailed in the protocol."

The fifth step is to determine the confidence in the evidence from the overall group of studies. "These ratings reflect confidence that the study findings accurately reflect the true association between exposure to a substance and an effect. . . . Conclusions developed in the subsequent steps of the method are based on the evidence with the highest confidence. . . . For each outcome, collections of studies are given an initial confidence rating by study design. . . . The initial rating is downgraded for factors that decrease confidence and upgraded for factors that increase confidence in the results. Then, confidence across all available study designs is assessed," according to the recommendations.

Next, the approach calls for "[t]ranslat[ing] confidence ratings into level of evidence for health effect . . . [which] is assessed separately within the human, experimental animal, and to the extent possible and necessary, other relevant data sets. The level of evidence for health effects conclusions reflect both the overall confidence in the association between exposure to the substance and the outcome (effect or no effect) and the direction of the effect (toxicity or no toxicity)."

Step seven is hazard identification. "To determine the hazard identification conclusion, the highest level of evidence for a health effect from each of the evidence streams is combined in the final step of the evidence assessment process. Hazard identification conclusions may be reached on individual outcomes (health effects) or groups of biologically related outcomes, as appropriate, based on the evaluation's objectives and the available data. . . . The four hazard identification conclusion categories are: Known to be a hazard to humans; Presumed to be a hazard to humans; Suspected to be a hazard to humans; [and] Not classifiable or not identified to be a hazard to humans," NTP says.

Following the release of the recommendations, ACC and SBA's Office of Advocacy raised concerns with what they claim is a lack of transparency in how NTP developed the approach.

ACC argues that NTP and BSC have not requested public comment on the developing approach, nor was a meeting of the BSC work group reviewing the draft approach publicly announced.

In a Nov. 27 letter, ACC includes a list of criticisms of the August draft of NTP's systematic-review approach. "The approach appears highly biased towards greater consideration of epidemiological data, when most toxicological data is experimental, *in vitro*, or uses animal models," Michael Walls, vice president of regulatory and technical affairs, writes in the letter. "Confidence in the 'body of evidence' does not appear to include consideration of plausibility, mode of action, or relevance of the dosing to environmental exposures that are of concern."

ACC also queries what it considers an over-reliance on human data at the expense of toxicology and other non-human data. "Evaluation of non-human data is not given sufficient weight or systematic consideration. . . . NTP has developed an approach that can start with studies of low quality but somehow lead to moderate or high confidence in the 'body of evidence' and thus based on these low quality studies, later conclude that the associations found imply a causal link."

Similarly, SBA's letter says the office "has heard from small businesses that are concerned that the very short time period NTP has provided for review of and comment on [the systematic-review approach] will negatively affect their interests and will not promote openness and transparency" required under Executive Order 13563. -- *Maria Hegstad*

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